

Racing to immunity: Journey to a COVID-19 vaccine and lessons for the future

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SARS-CoV-2 is the novel coronavirus behind the COVID-19 pandemic. Since its emergence, the global scientific community has mobilized to study this virus, and an overwhelming effort to identify COVID-19 treatments is currently ongoing for a variety of therapeutics and prophylactics. To better understand these efforts, we compiled a list of all COVID-19 vaccines undergoing preclinical and clinical testing using the WHO and ClinicalTrials.gov database, with details surrounding trial design and location. The most advanced vaccines are discussed in more detail, with a focus on their technology, advantages and disadvantages, as well as any available recent clinical findings. We also cover some of the primary challenges, safety concerns and public responses to COVID-19 vaccine trials, and consider what this can mean for the future. By compiling this information, we aim to facilitate a more thorough understanding of the extensive COVID-19 clinical testing vaccine landscape as it unfolds, and better highlight some of the complexities and challenges being faced by the joint effort of the scientific community in finding a prophylactic against COVID-19.

KEYWORDS

antiviral agents, coronavirus, coronavirus infections, COVID-19, COVID-19 drug treatment, immunosuppressive agents, pandemics, SARS virus, severe acute respiratory syndrome coronavirus 2, vaccines

1 | INTRODUCTION

At the end of 2019, a pneumonia of unknown aetiology emerged in Wuhan, China. Most patients presented to hospital with acute respiratory failure, and some developed severe complications.¹ The pathogen behind this disease (COVID-19, coronavirus disease 2019) was later identified as the novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2).² SARS-CoV-2 transmits primarily via air-borne respiratory droplets, and its spread is exacerbated by the prevalence of asymptomatic carriers.³ On 11 March 2020, the World Health Organization (WHO) declared COVID-19 a pandemic, and as of 25 November 2020, 59 481 313 cases have been confirmed across 220 countries, with 1 404 542 confirmed deaths.⁴

SARS-CoV-2 is a zoonotic member of the positive-sense single-stranded RNA (+ssRNA) coronavirus (CoV) family. Named for their crown-like surface **spike glycoprotein**, these viruses, which are capable of cross-species transmission, are genetically sub-divided into 4 genera; α CoV, β CoV, γ CoV, and δ CoV.⁵ Of the 7 zoonotic coronaviruses, 4 lead only to mild respiratory infection (accounting for 30% of common cold cases)⁶ while the other 3 (SARS-CoV, MERS-CoV [MERS, Middle Eastern respiratory syndrome] and SARS-CoV-2 [COVID-19]) have claimed international notoriety in the last 2 decades for their severe, sometimes fatal pathogenicity.

Although most COVID-19 cases are asymptomatic or accompanied only by mild, flu-like symptoms, certain populations—primarily in the elderly and individuals with underlying medical conditions—can develop acute lung injury and acute respiratory distress syndrome.⁷ Severely ill patients suffer not from viral cytopathogenicity, but as a result of cytokine storms, indicated by persistently high fevers, hypoxia and pneumonia, despite declining viral titres.⁸ As COVID-19

cases continue to rise and treatments limited to symptom management and supportive care, there is an undeniable need for a prophylactic solution capable of preventing or minimizing the severity of SARS-CoV-2⁹ (Figure 1).

In this review, we introduce the accelerated vaccine development pipeline, and consolidate the current state of COVID-19 vaccine trials with a focus on the most promising candidates. We discuss the advantages and disadvantages of different vaccine platforms. Finally, we address some of the challenges precipitated by the pandemic and what we can learn from them.

2 | UNDERSTANDING THE COVID-19 VACCINE DEVELOPMENT LANDSCAPE

Vaccine development is not a straightforward task; of the roughly 30 major human viral pathogens, vaccines have been approved for only 17.^{10,11} Viral biology, including genetic diversity, mutagenic rate, incubation period, and immunogenicity, can impede a vaccine's ability to produce neutralizing antibodies.^{12,13} Fortunately, SARS-CoV-2 is a good vaccine candidate, as most COVID-19 patients develop antibodies targeting the receptor binding domain (RBD) of the viral spike protein following infection, which are capable of neutralizing SARS-CoV-2.^{14,15} Therefore, all COVID-19 vaccines have been designed to target the viral spike RBD.

Immunization begins with the innate immune system, which recognizes viral surface proteins via pattern recognition Toll-like receptors (TLRs) on dendritic cells, macrophages, fibroblasts, and endothelial cells.¹⁶ Once activated, these cells endocytose and

disassemble the pathogen into smaller fragments (antigens),¹⁷ presenting them to T-cells and B-cells.¹⁶ Antibodies raised against these antigens are released into circulation, where they both bind and neutralize the target pathogen and enhance viral clearance by phagocytic cells.

Vaccine safety and efficacy is often inversely correlated; vaccines that resemble their viral target can more effectively activate the immune system to produce antibodies, but are also more likely to retain some level of viral cytopathogenicity.¹¹ To enhance the efficacy of vaccines, nonviral components termed adjuvants are often incorporated. Adjuvants can consist of aluminium salts, bacterial lipids or nucleic acids, and work by binding TLRs to trigger a robust immune response.¹⁸ Therefore, the majority of mild, self-resolving side effects associated with vaccination, including local inflammation, fever and nausea, are a natural consequence of immunization. In rare instances, certain adjuvant formulations can over-activate the immune system, leading to severe adverse effects. For example, build-up of aluminium-based adjuvants in the tissue may trigger allergy-like symptoms (by activating T_H2 and eosinophils), or chronic inflammation.¹⁹ It is therefore important to identify the right vaccine formulation via preclinical and clinical trials.

Many mild adverse effects are considered acceptable risks to vaccination, but severe reactions that enhance pathogen cytopathogenicity, like antibody-dependent enhancement and vaccine-associated enhanced respiratory disease (VAERD), must be avoided. Antibody-dependent enhancement occurs when a vaccine generates antibodies that bind but fail to neutralize its target pathogen. Upon post-vaccination infection, these non-neutralizing antibodies end up facilitating targeted infection of phagocytic immune cells, which

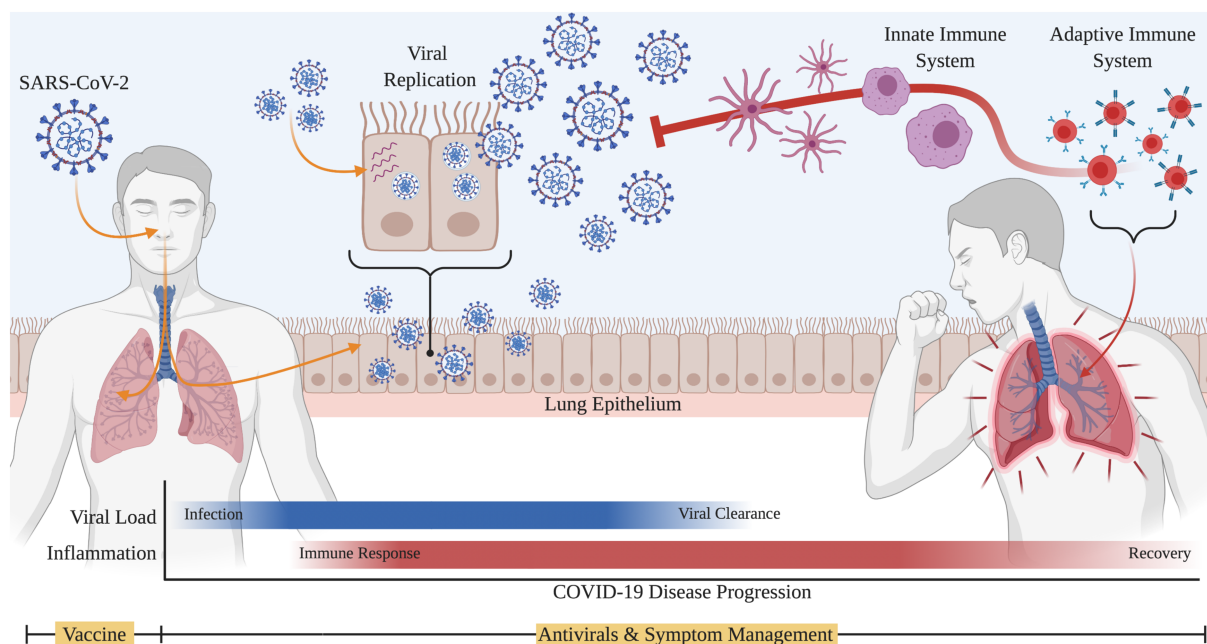


FIGURE 1 COVID-19 treatment strategies are dictated by disease progression. While antivirals, steroids, plasma therapy, and other drugs exist for the management of symptoms after infection, vaccines are only effective if administered prophylactically

respond by producing excessive amounts of proinflammatory cytokines, leading to severe inflammation.²⁰ VAERD was first clinically observed during a vaccine trial for respiratory syncytial virus (RSV), where vaccinated children developed an accumulation of neutrophils and lymphocytes in the lung upon RSV infection, and were therefore more likely to be hospitalized compared to unvaccinated children.²¹ While not mechanistically understood, VAERD correlates with inadequate neutralizing antibody production, inefficient cytotoxic T-cell activation, and inappropriate activation of T_H2 and eosinophils in the lung. Since VAERD is primarily seen in infants and young children, it is commonly attributed to low vaccine efficacy and immune system immaturity.²² Clinical trials must be carefully conducted to avoid these possible effects.

Traditionally, a vaccine may take at least 10 years from conception to implementation. Candidate vaccines are first tested preclinically with *in vitro* and animal models, to determine immunogenicity and toxicity. Then, they must complete 3 phases of clinical testing before being licensed: Phase I, which confirms vaccine immunogenicity; Phase II, which identifies appropriate dosing and immunization schedules; and Phase III, which tests for efficacy and safety in a larger pool of participants. To catch both short-term and long-term effects, each phase can last multiple years, and further pharmacovigilance (Phase IV) is conducted even after a vaccine enters the market. However, when the need for a vaccine is immediate, this process is accelerated by conducting different phases in parallel and shortening the length of each phase.²³ In response to COVID-19, the American Food and Drug Association (FDA) released acceptable trial design guidelines for accelerated vaccine development,²⁴ making it possible for promising vaccine candidates to apply for Emergency Use Authorization (EUA).²⁵ Unlike full licensing, completion of Phase III testing is not required for EUA

application, and instead the FDA can actively adjust vaccine implementation strategies in response to supplemental Phase III/IV results. A vaccine is considered successful if it has sufficient interim Phase III safety and efficacy data to show that it reduces the likelihood of developing COVID-19 by $\geq 50\%$ and “the known and potential benefits of the vaccine outweigh the known and potential risks”²⁵ (comparatively, the efficacy of the seasonal flu vaccine in the USA fluctuated between 19 and 60% between 2009 and 2019²⁶). As it is both dangerous and unethical to inoculate trial participants with SARS-CoV-2, vaccine efficacy is instead determined by comparing the number of COVID-19 cases in placebo-treated participants against that of vaccinated participants.

To consolidate the COVID-19 vaccine landscape, we extracted the list of preclinical and clinical vaccine trials from both the WHO database as well as ClinicalTrials.gov (Table S1) and noted the participant pool's size, age, and geographic region (Figure S1). In total, we identified 221 candidate vaccines being developed or tested for SARS-CoV-2 (Figure 2), and those in the most advanced stages of human trials are discussed in further detail (Figure 3). These vaccines can be broadly classified into 4 groups based on their components: traditionally inactivated or weakened viruses; viral vectors; nucleic acids; and viral proteins. In addition, we introduce some current efforts to repurpose existing vaccines for COVID-19.

2.1 | Live attenuated or weakened virus vaccines

Traditionally, vaccines licensed for human use consisted of viruses that were inactivated or weakened via mutagenesis or neutralizing chemical treatments (e.g. formaldehyde, β -propiolactone).^{27–29} Since these vaccines physically resemble live virus, they can elicit strong,

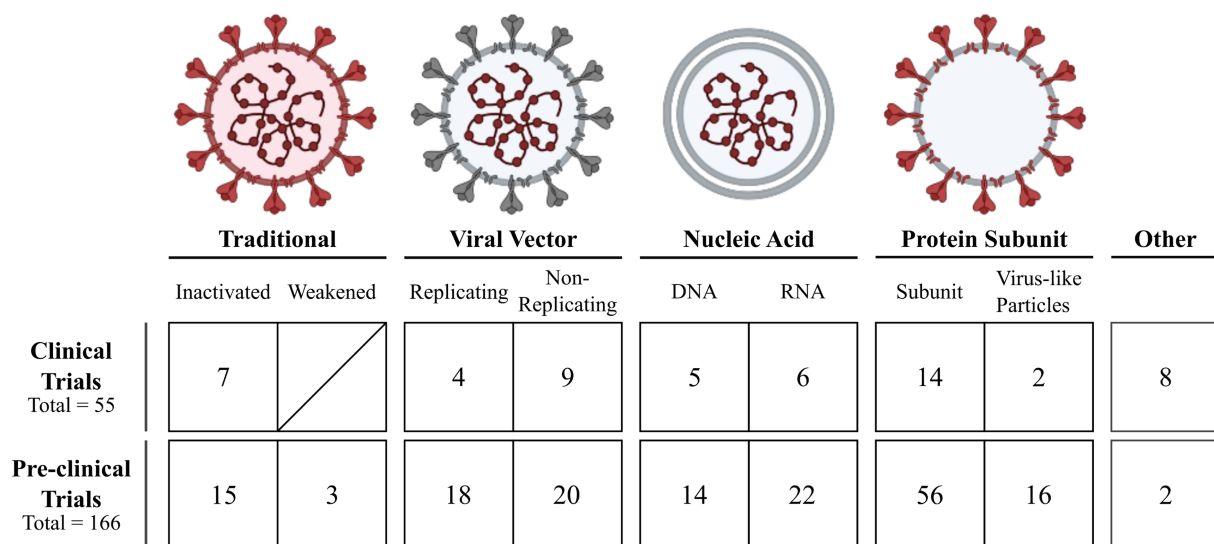


FIGURE 2 COVID-19 vaccines currently under development. A total of 221 vaccines are currently in active development, with 55 in clinical trials and the other 166 in preclinical evaluation. They are displayed here grouped by vaccine type. In the schematic for each vaccine design, any SARS-CoV-2 material present in the vaccine is shown in red to better highlight the similarities and differences of each vaccination approach




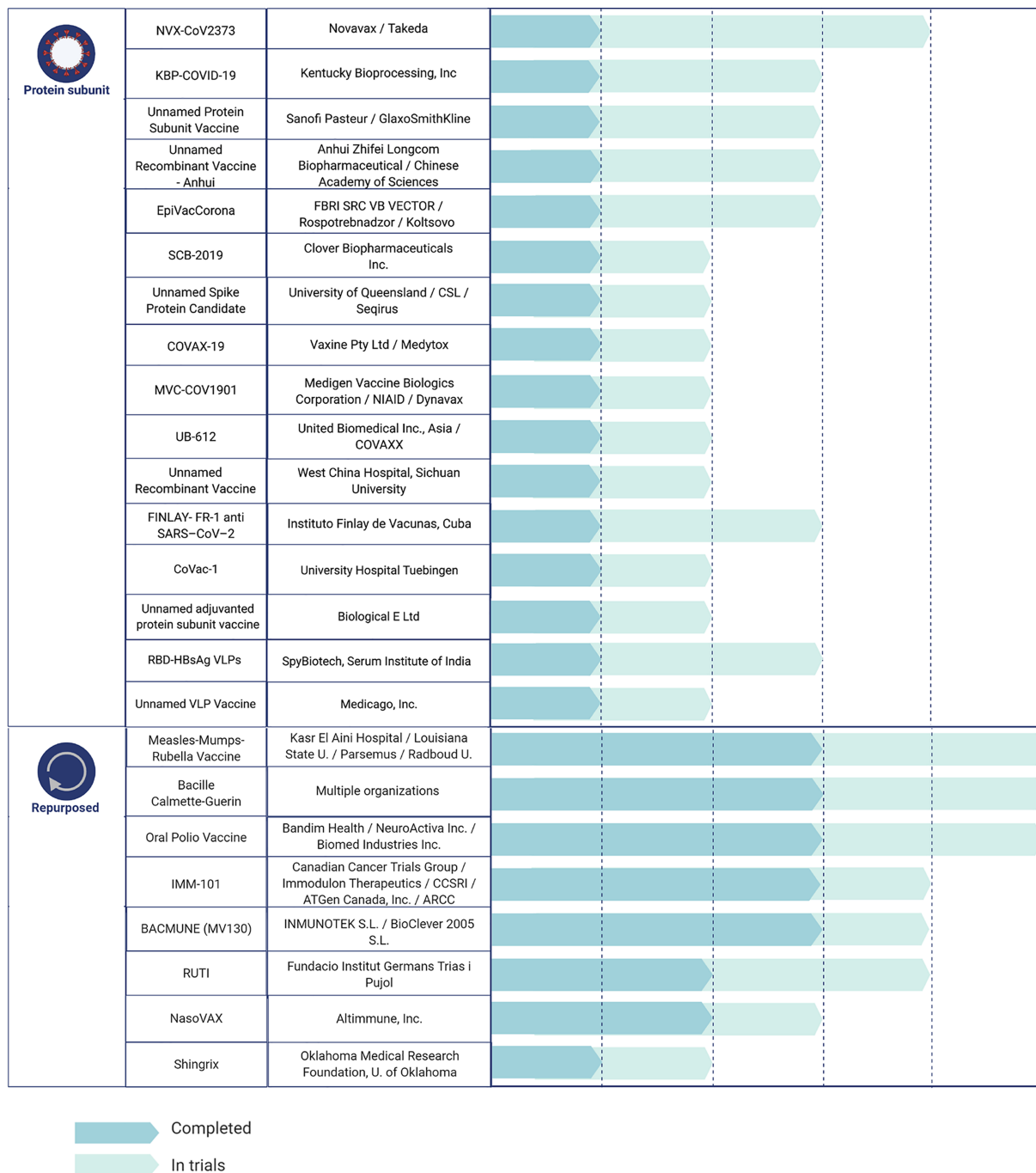
	Candidate	Developer/Manufacturer	Pre-clinical	Phase 1	Phase 2	Phase 3	Phase 4
 <p>Traditionally inactivated or weakened virus</p>	CoronaVac	Sinovac Biotech Co.	Completed	Completed	Completed	Completed	
	Unnamed Inactive Vaccine - Wuhan	Wuhan Institute of Biological Products / Sinopharm	Completed	Completed	Completed	Completed	
	BBIBP-CoV	Beijing Institute of Biological Products / Sinopharm	Completed	Completed	Completed	Completed	
	BBV152A, B, C	Bharat Biotech International Limited	Completed	Completed	Completed	Completed	
	QazCovid-in	RIBSP, Republic of Kazakhstan	Completed	Completed	Completed	Completed	
	Unnamed Inactive Vaccine - Yunnan	Chinese Academy of Medical Sciences	Completed	Completed	Completed	Completed	
	Unnamed inactivated SARS-CoV-2 Vaccine	Beijing Minhai Biotechnology Co., Ltd.	Completed	Completed	Completed	Completed	
 <p>Viral Vector</p>	AZD1222 (ChAdOx1 nCoV-19)	University of Oxford/AstraZeneca	Completed	Completed	Completed	Completed	
	Ad5-nCoV	CanSino Biological Inc. / Beijing Institute of Biotech	Completed	Completed	Completed	Completed	
	Gam-COVID-Vac (rAd26-S+rAd5-S)	Gamaleya Research Institute	Completed	Completed	Completed	Completed	
	Ad26.COV2.S	Janssen Vaccines and Prevention Pharmaceutical Companies	Completed	Completed	Completed	Completed	
	DeiNS1-2019-nCoV-RBD-OPT1	Beijing Wantai Biological Pharmacy / Xiamen University	Completed	Completed	Completed	Completed	
	IIBR-100	Israel Institute for Biological Research	Completed	Completed	Completed	Completed	
	TMV-083	Institute Pasteur/Themis/ U. of Pittsburg / Merck Sharp & Dohme	Completed	Completed	Completed	Completed	
	GRAd-COV2	ReiThera Srl / INMI Lazzaro Spallanzani	Completed	Completed	Completed	Completed	
	Ad5-nCoV	Institute of Biotech/Academy of Military Medical Sciences	Completed	Completed	Completed	Completed	
	Oral SARS-CoV-2 VX (VXA-CoV2-1)	Vaxart	Completed	Completed	Completed	Completed	
	MVA-SARS-2-S	Ludwig-Maximilians - University of Munich	Completed	Completed	Completed	Completed	
	hAd5-S-Fusion+ N-ETSD	Immunity BIO, Inc.	Completed	Completed	Completed	Completed	
	V590	Merck Sharp & Dohme Corp.	Completed	Completed	Completed	Completed	
	 <p>Nucleic acids (RNA/DNA vaccines)</p>	mRNA-1273	ModernaTX, Inc. / NIAID	Completed	Completed	Completed	Completed
BNT162(b1,b2,b3) (3 LNP-mRNAs)		Biontech SE / Pfizer / Shanghai Fosun Pharmaceuticals	Completed	Completed	Completed	Completed	
CVnCoV (mRNA)		CureVac AG / CEPI	Completed	Completed	Completed	Completed	
LUNAR-COV19 (ARCT-021) (RNA)		Arcturus Therapeutics, Inc. / Duke-NUS	Completed	Completed	Completed	Completed	
LNP-nCoVsaRNA		Imperial College London	Completed	Completed	Completed	Completed	
Unnamed mRNA vaccine		PLA Academy of Military Sciences / WalvaxBiotech	Completed	Completed	Completed	Completed	
INO-4800 (DNA)		Inovio / International Vaccine Institute	Completed	Completed	Completed	Completed	
AG0301-COVID19 (DNA)		Osaka University / AnGes / Takara Bio	Completed	Completed	Completed	Completed	
ZyCoV-D (DNA)		Zydus Cadila / Cadila Healthcare Limited	Completed	Completed	Completed	Completed	
GX-19 (DNA)		Genexine, Inc.	Completed	Completed	Completed	Completed	
bacTRL-Spike (DNA)		Symvivo Corporation	Completed	Completed	Completed	Completed	

FIGURE 3 The current landscape of clinical trials for the 50 most advanced vaccines for COVID-19. Of the 2021 vaccines currently being studied, 166 are in preclinical stages and 55 are in ongoing human trials. Showcased in this figure are the 55 most promising vaccines in different clinical stages under 5 different categories, based on the technology used for vaccine development. Shown in light blue are the current ongoing trials and shown in darker blue are the completed preclinical or clinical trials


FIGURE 3 (Continued)

protective immune responses. However, care must be taken to fully eliminate viral cytopathogenicity before use.

To manufacture inactivated viral vaccines *en masse*, large amounts of infectious material is needed. Live viral samples are usually collected from multiple patients and replicated in Vero cells, an African green monkey cell line that is susceptible to infection.³⁰ The strain with the best proliferative ability and lowest mutagenesis rate is then isolated, further proliferated, and inactivated to generate the vaccine. There are currently 7 inactivated SARS-CoV-2 vaccines undergoing advanced clinical trials (Figure 3).

2.1.1 | CoronaVac (previously PiCoVacc)

Beijing-based pharmaceutical company Sinovac Biotech's CoronaVac vaccine combines a SARS-CoV-2 sample sourced from a Chinese hospitalized patient with aluminium adjuvant.³¹ In initial animal studies, CoronaVac was found to induce the production of neutralizing antibodies against SARS-CoV-2 in mice and rats.³¹ Triple 3- or 6- μ g doses of the vaccine also protected against subsequent viral challenge in rhesus macaques, a nonhuman primate capable of developing age-dependent pneumonia in response to

SARS-CoV-2.^{31,32} No immunopathological exacerbations were observed. In Phase I/II trials, results showed that 2 3- μ g doses administered either 14 or 28 days apart resulted in seroconversion in 92.4 and 97.4% of the participants when measured 2 and 3 weeks later, respectively.³³ In addition, neutralizing antibody titres decreased with participant age (18–59 y), and both doses were well tolerated.³³ A Phase III clinical trial enrolling frontline healthcare professionals launched in Brazil on 2 July 2020 (PROFISCOV, ClinicalTrials.gov NCT04456595) followed by trials in Indonesia (NCT04508075) and Turkey (NCT04582344). In China, CoronaVac is already approved for emergency use by essential workers and high risk individuals,³⁴ and Phase I/II trials are underway to determine its safety and immunogenicity in both children over 3 years and adults over 60 years (ClinicalTrials.gov NCT04551547, NCT04383574, NCT04617483).

2.1.2 | Unnamed inactive vaccine—Wuhan

The Chinese pharmaceutical company Sinopharm is developing an inactivated vaccine with the Wuhan Institute of Biological Products. Currently unnamed, this vaccine uses a SARS-CoV-2 strain isolated from a patient at Wuhan's Jinyintan Hospital, and is enhanced with aluminium adjuvant.³⁵ It was also the first inactivated vaccine to initiate Phase III testing.

Phase I trials in which 72 participants (18–59 y) received either triple doses of 2.5 μ g, 5 μ g, or 10 μ g vaccine reported 97% seroconversion 2 weeks after the final injection.³⁵ Interim analysis from a Phase II trial conducted in parallel showed that 2 doses of 5 μ g administered across 14 or 21 days achieved similar immunogenicity outcomes (41 out of 42 vaccinated participants, 97.6%).³⁵ Both trials reported a low rate of mild adverse reactions, with the most common being pain at the site of injection and fever.³⁵ In June, Phase III trials began with 15 000 participants in the United Arab Emirates (UAE; Chinese Clinical Trial Registry, ChiCTR2000034780), and has since expanded to Jordan, Bahrain (ClinicalTrials.gov, NCT04510207), and Morocco (ChiCTR2000039000) for an estimated total of 45 600 participants. On 14 September 2020, the UAE approved the use of this vaccine as an emergency prophylaxis for healthcare workers.³⁶

2.1.3 | BBiBP-CorV

Sinopharm is also working with the Beijing Institute of Biological Products to create a second inactivated vaccine with aluminium adjuvant, BBiBP-CorV.³⁷ In preclinical trials, 2 2- μ g doses induced sufficient levels of neutralizing antibody in 6 mammalian species, including rhesus macaques, and protected against subsequent SARS-CoV-2 challenge.³⁷ A total of 192 participants in Phase I trials received 2 doses of 2, 4 or 8 μ g vaccine, which were well-tolerated and triggered only dosage-dependent mild adverse reactions.³⁸ While all participants had neutralizing antibodies by 28 days, larger doses

resulted in earlier seroconversion, and the vaccine's immunogenicity did not drop with participant age.³⁸ Subsequent Phase II trials tested either a single 8- μ g dose or 2 4- μ g doses administered either 14 days or 28 days apart. Those who received 2 doses 28 days apart had the highest antibody titres after 3 weeks compared to the other treatment groups.³⁸ Phase III trials are underway in the UAE, Jordan, Egypt, and Bahrain alongside the unnamed Wuhan vaccine mentioned above (ClinicalTrials.gov NCT04510207), and a separate Phase III trial for 3000 participants began 23 September in Argentina (NCT04560881).

2.2 | Replicating or nonreplicating viral vector vaccines

While live attenuated vaccines are made with intact viruses, viral vector vaccines consist of an replication-deficient or attenuated replication-competent human or chimpanzee adenovirus containing the DNA of the target pathogen's surface protein.²⁷ In the case of COVID-19, the spike protein gene is the only component of SARS-CoV-2 incorporated into these vaccines. While only a few viral-vectored vaccines have been approved for viral infections, this platform has been extensively investigated for cancer treatment. Unlike inactivated vaccines, viral vector vaccines have lower cytotoxicity risk (as even nonattenuated adenoviruses only cause mild cold or flu) but are still recognized as viruses by TLRs.³⁹ However, certain populations, especially in developing countries, may already be immune to these viruses. For example, natural seroprevalence for the commonly used human adenovirus 5 (Ad5) and chimpanzee adenovirus (ChAd), is between 60 and 90%,⁴⁰ and 1 and 19%^{41,42} respectively, with consistently higher rates in Asian and African populations. For these reasons, the efficacy of viral vector vaccines may vary between different ethnic groups.

2.2.1 | ChAdOx1 nCoV-19 (AZD-1222)

Developed by Oxford University and AstraZeneca, ChAdOx1 nCoV-19 is made by fusing the SARS-CoV-2 spike gene to the replication defective chimpanzee adenovirus ChAdOx1.⁴³ This design is based on recent Phase I results with ChAdOx1-based vaccines for tuberculosis (TB) and MERS.^{44,45} A single dose generated neutralizing antibodies in mice and rhesus macaques that reduced disease severity and viral load in the lower respiratory tract after subsequent SARS-CoV-2 challenge, but did not prevent infection.⁴⁶

Phase I/II trials were conducted with 2 doses of 5×10^{10} viral particles across 28 days. 91% of participants seroconverted after the first dose, and all participants had neutralizing antibodies after the second.⁴⁷ The vaccine was well-tolerated.⁴⁷ Following these findings, Phase III trials were approved in the USA in August (ClinicalTrials.gov NCT04516746) for 30 000 participants. Phase II/III trials are also being held in the UK (NCT04400838), South America (NCT04516746, NCT04536051), Japan (NCT04568031), and South Africa

(NCT04444674), where the vaccine's efficacy will be tested in human immunodeficiency virus-positive participants.

On 6 September, all trials were paused after a participant allegedly developed transverse myelitis,^{48,49} a rare but severe neurological condition in which inflammation along the spinal cord results in pain, muscle weakness and paralysis. Transverse myelitis has been linked to vaccines for hepatitis B, measles, and diphtheria in rare instances,⁵⁰ and 1 case was reported in 2009 in response to the H1N1 vaccine.⁵¹ While news of the initial hold was seen as evidence of scientifically rigorous testing,⁴⁸ AstraZeneca's decision to restart trials in the UK on 14 September without disclosing results from the safety investigation triggered calls for transparency and fuelled growing suspicions over vaccine safety in the USA and UK.^{52,53} After reviewing all safety data, the FDA re-authorized ChAdOx1 nCov-19 trials in the USA on 23 October, marking the complete resumption of all AstraZeneca trials globally.⁵⁴

On 23 November, AstraZeneca announced Phase III interim analysis results, in which the vaccine was reported to be 90% effective when administered in 2 doses of 2.5×10^{10} and 5×10^{10} viral particles at least 1 month apart, and 62% efficacy when administered as 2 doses of 5×10^{10} viral particles at least 1 month apart.⁵⁵ Of the 131 COVID-19 cases identified, vaccinated participants with COVID-19 did not experience severe symptoms or require hospitalization. The report also claimed that no vaccine-triggered severe adverse events have been reported. As with most vaccines, ChAdOx1 nCov-19 can be stored and transported at regular refrigeration temperatures (2–8°C) and last at least 6 months.⁵⁵

2.2.2 | Ad5-nCoV

The Chinese vaccine company CanSino Biologics is developing a viral vector vaccine using a replication-defective form of the human adenovirus Ad5 and the SARS-CoV-2 spike gene. During preclinical trials, Ad5-nCoV sufficiently protected ferrets and mice from SARS-CoV-2 challenge.⁵⁶ In subsequent Phase I trials, the vaccine was tested at 3 different doses (5×10^{10} , 1×10^{11} and 1.5×10^{11} viral particles), and dose-dependent titres of neutralizing antibodies were detected by day 14.⁵⁷ Since those who received the highest dose experienced higher reactogenicity including reports of severe fever, fatigue, dyspnoea, muscle pain and joint pain,⁵⁷ Phase II trials focused on the 2 lower doses, and confirmed that both could induce seroconversion and were well-tolerated.⁵⁸ This vaccine is currently undergoing Phase II testing in children ≥ 6 years and adults ≥ 56 years in China (NCT04566770), and Phase III trials in Russia (NCT04540419) and Pakistan (NCT04526990).

2.2.3 | Ad26.COVS.2S

Johnson & Johnson is developing the viral vector vaccine Ad26.COVS.2S using Ad26, a human adenovirus that has lower natural seroprevalence rates than Ad5 (43–68% in African populations).^{41,59}

The vaccine effectively protected rhesus macaques and hamsters from SARS-CoV-2 challenge in preclinical trials.^{60,61} Phase I/II trials identified single doses of 5×10^{10} or 1×10^{11} viral particles sufficient to trigger neutralizing antibodies in 92% of participants a month after vaccination.⁶² Two Phase III trials are being conducted; the first, which began on 10 August, is testing single doses of 1×10^{11} viral particles on 60 000 participants within the USA, South America, Southeast Asia, South Africa and parts of Europe (ENSEMBLE, ClinicalTrials.gov NCT04505722), while a second is testing a 2-dose regimen in the UK, France, the USA and South Africa (ENSEMBLE2, NCT04614948).

On 12 October, Johnson & Johnson placed a temporary pause on all clinical trials in response to an unexplained illness in a study participant. This pause was lifted on 23 October with FDA approval, after an independent investigation found no connection between it and the vaccine.^{63,64} At time of writing, no details have been released regarding the nature of the illness.

2.2.4 | Gam-COVID-Vac (sputnik V)

Gam-COVID-Vac is a COVID-19 vaccine being developed by Russia's Gamaleya Research Institute of Epidemiology and Microbiology. Unlike other viral vector vaccines, Gam-COVID-Vac is a heterologous formulation consisting of 2 human adenovirus vectors, Ad26 and Ad5, both carrying the SARS-CoV-2 spike gene. Phase I/II trials from June found that a single dose of 1×10^{11} viral particles triggered seroconversion in all 76 participants by 42 days postinjection.⁶⁵ Despite doubt from the scientific community, the vaccine gained regulatory approval in Russia on 11 August.⁶⁶ In September, Phase III trials began in Russia with 40 000 participants (RESIST, ClinicalTrials.gov NCT04530396) in which the vaccine was administered in 2 doses 21 days apart, and on October 27th, Gam-COVID-Vac became the first COVID-19 vaccine submitted to the WHO for approval.⁶⁷ In an interim report published on 22 November, Gamaleya claimed its vaccine was 92% effective after the first dose based on 20 COVID-19 cases across 16 000 participants.⁶⁸ By 24 November, updated reports describe the vaccine as being 91% and 95% effective at 7 and 21 days respectively, and after both doses have been administered, based on a total of 39 confirmed COVID-19 cases.⁶⁹ Both reports note the absence of unexpected adverse effects, and Gamaleya intends to release a third interim analysis once 78 COVID-19 cases have been recorded.^{68,69} These results have yet to be formally published.

2.3 | Nucleic-acid vaccines (DNA/RNA)

Gene-based approaches to vaccine development represent a new way of approaching immunization.⁷⁰ By directly introducing fragments of viral genomic material in the form of DNA or RNA into host cells, these vaccines provide cells with the information necessary to express and present viral antigens to the immune system. Since only the viral

genetic sequence is required, nucleic acid vaccines are cheap, safe, and relatively easy to design and manufacture. However, this strategy comes with its own set of unique challenges. Although the structure of DNA contributes to its stability, RNA is chemically reactive and therefore prone to self-cleavage and degradation by ribonucleases, and while these vaccines are stabilized inside lipid nanoparticles,⁷⁰ RNA vaccines remain much more vulnerable compared to vaccines containing DNA, protein or whole viral particles.⁷¹ For this reason, the temperature and storage conditions of RNA vaccines needs to be determined empirically, and more regulation will probably be necessary for distribution and administration. DNA vaccines are also uniquely complicated; unlike other vaccines, DNA vaccines must enter the cell nucleus to drive antigen expression. Since the nuclear membrane is less porous than the plasma membrane, these vaccines must be administered with a gene gun,²⁷ which also must be tested to ensure efficacy and safety.

While recombinant plasmid DNA has been explored as a vaccine platform for decades, the possibility of using RNA for human vaccine development is rather new.⁷¹⁻⁷³ To date, only a few RNA-based treatments are in use, including the small interfering RNA (siRNA) therapies Givlaari (givosiran) for acute hepatic porphyria⁷⁴ and Onpattro (patisiran) for polyneuropathy of hereditary TTR-mediated amyloidosis.⁷⁵ While nucleic acid vaccines hold promise, the relative lack of existing DNA/RNA prophylactics mean that relatively less is known about its safety profile, reliability, and feasibility compared to other vaccine platforms.

2.3.1 | BNT162b2 vaccine

BioNTech, a German pharmaceutical company, is currently pursuing the development of its nucleoside-modified mRNA vaccine BNT162b2 in partnership with Pfizer. BNT162b2 consists of the full-length SARS-CoV-2 spike protein mRNA encased in a lipid nanoparticle. In Phase I, this vaccine triggered neutralizing antibodies titres 1.8–2.8 times higher than titres seen in recovered COVID-19 patients.⁷⁶ In addition, both Phase I and II trials revealed only mild to moderate side effects, including fever, chills and fatigue, and identified a 2-dose regimen across 21 days as the most appropriate for subsequent trials.⁷⁷ Phase III trials began in Germany in May (ClinicalTrials.gov NCT04537949) followed by additional Phase II/III trials in the USA, parts of South America and South Africa (NCT04365728). In August, Phase I trials were approved in China (NCT04523571). On 12 October, Pfizer announced that Phase III trials in the USA were being expanded to include children as young as 12 years, making it the first US/European-based COVID-19 vaccine tested in individuals younger than 18 years.⁷⁸ Although COVID-19 hospitalization and mortality rates are lowest in this age group, 10.7% of US COVID-19 cases occur in children, making them significant sources of viral spread.⁷⁹

On 9 November, Pfizer announced initial Phase III interim reports describing its vaccine as having up to 90% efficacy against SARS-CoV-2.⁸⁰ By 18 November, the company officially concluded

its Phase III trial⁸¹ and reported its vaccine as being 95% effective. A total of 170 COVID-19 cases were identified in 43 661 participants tested 7 days after completing the treatment or placebo. Of these, 162 cases belonged to the placebo group, and 8 from vaccinated participants. Furthermore, of the 10 severe COVID-19 cases observed, 9 occurred in the placebo group.⁸¹ The report also stated a lack of severe safety concerns across its ethnically diverse participant pool, and consistent vaccine efficacy across sex and race demographics. The vaccine was similarly effective in participants ranging from 18 to 85 years.⁸¹ As BNT162b2 was empirically determined to be most stable at -70°C ,⁸¹ the company is currently working to establish reliable cold-chain distribution and storage methods. This report does not discuss the vaccine's efficacy in individuals with comorbidities. As of time of writing, Pfizer has applied for EUA with the FDA and is preparing to manufacture 50 million doses of this vaccine by the end of 2020.⁸¹

2.3.2 | mRNA-1273

American biotech company Moderna is home to mRNA-1273, which consists of the SARS-CoV-2 spike protein's mRNA encapsulated in a lipid nanoparticle.^{82,83} Designed only 45 days after the SARS-CoV-2 genome was sequenced, mRNA-1273 elicited neutralizing antibodies in a dose-dependent fashion within 2 weeks of vaccination in Phase I trials.⁸³ Three immunization regimens were tested: 2 injected doses of 25 or 100 μg , and a single 250- μg dose. While no serious vaccine-related adverse events were reported, $\geq 50\%$ of participants experienced mild events including fatigue, chills, headache, myalgia and pain at the injection site, and the single concentrated dose correlated with more moderate adverse events. Subsequent Phase II testing determined that 2 doses of 100 μg was most appropriate (ClinicalTrials.gov NCT04405076) and Phase III trials, which began recruiting on 14 July across the USA, prioritized high-risk individuals including healthcare workers and those with underlying medical conditions (COVE, NCT04470427).

On 16 November, and with 30 000 participants enrolled, Moderna's mRNA vaccine became the second of its kind to release interim Phase III analysis.⁸⁴ In total, 95 COVID-19 cases were identified in participants tested 2 weeks after the second injection. Of these, 90 came from the placebo group, and 5 from the vaccinated group. Importantly, 11 cases were described as being *severe*, all of which came from the placebo group. Based on these results, Moderna concluded its vaccine to be 94.5% effective. Up to now, there have been no reports of severe adverse effects, and no safety concerns have been raised.⁸⁴ This report also emphasized the ethnic and medical diversity of the participants tested, of which 37% belonged to communities of colour, and 42% were high-risk due to existing comorbidities.⁸⁴ The vaccine appears to be stable for up to a month in a standard refrigerator ($2-8^{\circ}\text{C}$), and can be stored for up to 6 months at standard freezer temperatures (-25 to -15°C),⁸⁵ making it less challenging to administer compared to Pfizer's mRNA vaccine. The trial intends to be maintained until at least 151 COVID-19 cases are

identified, and participants will be followed up with continued testing until 2 months post-treatment.

2.3.3 | DNA-based vaccines

Of the 4 DNA-based COVID-19 vaccines in clinical trials, none have advanced to Phase III trials (Figure 3) and little is known about their efficacy. For example, INO-4800, which contains the spike protein gene, is currently being developed by US biotechnology company Inovio Pharmaceuticals. Preclinical results in mice and guinea pigs examined the vaccine's immunogenicity.⁸⁶ As a proof of concept, a separate group independently created a DNA vaccine with the same genetic material, and reported that it could elicit neutralizing antibody production in rhesus macaque which protected against (but did not prevent) subsequent SARS-CoV-2 challenge.⁸⁷ Interim Phase I results reported by the company stated neutralizing antibodies were induced in 94% of participants (40 total), with no significant safety concerns.⁸⁸ On 16 November, Phase II/III trials were announced to further test the safety and efficacy of both INO-4800 as well as the gene gun being used to administer this vaccine directly through the skin, but as of writing, recruitment has not yet begun.⁸⁹

2.4 | Protein-based: Protein subunits or virus-like particles

In direct contrast to other vaccine approaches, protein-based vaccines contain only viral proteins without any genomic material, and therefore run no risk of becoming infectious.⁹⁰ These vaccines are made either with protein subunits (fragments of viral surface protein) or virus-like particles (nanostructures that resemble the outer viral envelope).

Protein subunit vaccines contain recombinant viral surface proteins packaged in a way that mimics the viral target. For these vaccines, the protein is made and purified from nonmammalian systems using laboratory methods and assembled *in vitro*. While this design permits more control over the shape and density of the viral proteins presented to the immune system, these vaccines are also more sensitive to improper epitope conformations.^{91,92} Previously, protein-based vaccines containing the spike protein RBD from both SARS-CoV-1 and MERS-CoV showed promising seroconversion of animal models. Currently, there are 14 COVID-19 subunit vaccines in clinical trials (Figure 3), and 54 other candidates under preclinical development, making this the most commonly studied vaccine platform for COVID-19.

While also assembled *in vitro*, virus-like particles (VLPs) differ in that they consist of multiple different viral structural proteins. In the case of SARS-CoV-2, VLPs contain the spike protein coassembled with the M, E and sometimes N coronavirus envelope proteins, all purified from eukaryotic expression systems.^{91,92} Several approved commercial vaccines, including those for human papillomavirus and hepatitis B, are based on VLPs, so its biology and safety profiles are

well-established, and they can be safely and easily mass-produced.⁹³ To date, only 2 COVID-19 VLP vaccines are in clinical testing: RBD-HBsAg VLP and an Unnamed VLP vaccine, in Phase I/II and Phase I respectively.

2.4.1 | NVX-CoV2373

NVX-CoV2373 is a protein subunit vaccine developed by Novavax, consisting of the SARS-CoV-2 spike protein, and is the most advanced COVID-19 vaccine with this platform. The vaccine is formulated with Novavax's patented Matrix-M adjuvant, a saponin-based adjuvant that stimulates entry of antigen-presenting cells into the injection site to enhance immune system activation^{94,95} to produce stronger, long-lasting immune responses. Novavax recently announced results from Phase I/II trials showing that the vaccine was well-tolerated and that 2 doses of 5 µg was sufficient to induce neutralizing antibody titres exceeding those found in convalescent serum from symptomatic Covid-19 patients.^{94,96} In October, Novavax began Phase III clinical trials in the UK with healthy adult participants (ClinicalTrials.gov NCT04583995), and in November, additional Phase III trials were initiated in the USA and Mexico to recruit high-risk participants (NCT04611802).

2.5 | Repurposed

Alongside global efforts to develop and test COVID-19 vaccines, various groups have been exploring the possibility of repurposing existing vaccines for COVID-19. These efforts are built upon prior knowledge of vaccine nonspecific effects (NSEs).

NSE is a phenomenon by which the administration of 1 vaccine improves or impairs one's response to unrelated pathogens, probably because the vaccine modified components of the immune system.⁹⁷ Vaccine NSEs were first recognized in the 1970s, when the introduction of a live attenuated measles vaccine to low-income countries led to reductions in mortality in vaccinated children that could not be explained by protection against measles infection alone.⁹⁸ Since then, numerous observational studies in children from both low-income and high-income settings show that immunization with live attenuated vaccines, such as those against measles, smallpox, TB and polio can have broad beneficial NSEs while immunization using nonlive vaccines, including inactivated vaccines for polio, diphtheria-tetanus-pertussis, hepatitis B and seasonal influenza, do not.⁹⁸ In some cases, childhood immunization with nonlive vaccines has been shown to actually increase susceptibility to unrelated infections in girls; however, the same effect have not been found in boys.⁹⁸ In cases where live and nonlive vaccines were administered in combination, the vaccine administered last dictated NSEs, and individuals with prior immunity to the targeted pathogen can still experience NSEs upon re-vaccination.⁹⁸ Based on these findings, clinical trials are underway to determine if existing live-attenuated vaccines can protect against SARS-CoV-2. Since these vaccines are already

FDA-approved, have known safety profiles, and are generally accessible as they are routinely administered around the world, they can be easily repurposed as temporary prophylactics if a COVID-19 vaccine is unavailable.

2.5.1 | Measles–mumps–rubella vaccine

The measles–mumps–rubella (MMR) vaccine, is a cocktail comprised of live-attenuated strains of the 3 highly contagious RNA viruses that, while not incurable, can trigger a host of serious health complications.⁹⁹ Developed in the 1970s, the MMR is the main vaccine provided worldwide to protect against these viruses. In the USA, the CDC recommends the MMR vaccine to be administered to children before age 6 years, as well as to high-risk adults (i.e. health care workers). Studies of children in the USA,¹⁰⁰ Italy,¹⁰¹ Denmark^{102,103} and the Netherlands¹⁰⁴ show that children who were most recently vaccinated with MMR had reduced rates of hospital admissions for other respiratory illnesses, including RSV, compared to children who were most recently vaccinated with nonlive vaccines.

The SARS-CoV-2 spike protein is 20% identical to that of the rubella virus, and COVID-19 patients with higher circulating rubella antibodies reportedly experience lower SARS-CoV-2 viral burden.¹⁰⁵ Additionally, 2 unreviewed epidemiological studies suggest a negative correlation between MMR immunization rates and COVID-19 rates and symptom severity, both globally and across 37 North American and European countries.^{106,107} The same trends were not found between COVID-19 and diphtheria–tetanus–pertussis immunization rates.¹⁰⁷ The Washington University School of Medicine is leading the effort to determine if MMR protects against COVID-19 infection through a Phase III trial (CROWN CORONA, ClinicalTrials.gov NCT04333732) in healthcare workers.

2.5.2 | Bacille Calmette–Guerin vaccine

The Bacille Calmette–Guerin (BCG) vaccine is a live-attenuated vaccine containing the bacteria *Mycobacterium bovis*, which was isolated in 1900 from the milk of a cow with bovine TB and attenuated by repeated passaging on potatoes.¹⁰⁸ Today, it remains the main prophylactic treatment for human TB. The BCG vaccine is usually administered intradermally on the upper arm, where it leaves behind a small scar. Unlike MMR, the efficacy of BCG against TB is disputable, and has been reported to fall anywhere from 0 to >80%¹⁰⁹ due to the heterogenous nature of TB as well as variations between different attenuated *M. bovis* cultures around the world.¹¹⁰ For this reason, BCG vaccine administration policies differ significantly between regions; in most of Asia, Africa and South America, BCG is universally administered to newborns, while in Australia, as well as parts of Europe and North America, it is only recommended for at-risk communities.¹¹⁰

The broad beneficial NSE of BCGs have been well documented worldwide, as immunization correlates with lower neonatal mortality

rates than can be expected from protection against TB alone.^{111–113}

Furthermore, BCG appears to confer nonspecific, potentially long-lasting protection against lower respiratory tract infections.^{114,115} However, given that BCG is usually not administered to adults, it is unclear if these benefits exist in later life. Epidemiological analysis of socially similar European countries and communities in Japan identified a negative correlation between BCG vaccination levels and COVID-19 mortality.^{116,117} Globally, BCG-vaccinated countries appears to have lower COVID-19 prevalence rates compared to countries without a BCG vaccination programme.^{118,119} To determine if BCG protects against COVID-19 infection in adults, Phase III studies with healthcare workers are currently underway in multiple countries, including the Netherlands (BRACE, ClinicalTrials.gov NCT04327206) and Australia (BCG-CORONA, NCT04328441).

2.5.3 | Oral polio vaccine

The oral polio vaccine (OPV) is made by combining attenuated versions of the 3 poliovirus serotypes behind poliomyelitis.¹²⁰ Vaccination for the poliovirus, which, like SARS-CoV-2, is a +ssRNA virus, can occur at any age and communities in polio-prone regions often receive regular booster doses.¹²¹ Unfortunately, while OPV is effective against poliomyelitis, it has been known to *de-attenuate* and create a vaccine-generated poliovirus that, over time, can trigger a polio outbreak similar to that created by regular poliovirus. Because of this, proper eradication of the poliovirus requires a 2-pronged approach; an initial treatment with the attenuated OPV, followed by secondary treatment using an inactivated, injectable polio vaccine to eliminate the potential development of vaccine-generated poliovirus. As OPV is cheaper and easier to produce, transport and administer compared to injectable polio vaccine, it is much more accessible, which is 1 of the reasons why polio continues to persist in certain developing countries.¹²¹ Similar to the other live-attenuated vaccines introduced above, the NSEs of OPV are largely beneficial, ranging from general reduction in infant mortality,^{122–124} to protection against childhood diarrhea¹²⁵ and ear infections.¹²⁶ Phase III trials testing the effect of OPV on COVID-19 rates are currently underway in the USA (OPV-NA831, ClinicalTrials.gov NCT04540185) and Guinea-Bissau (NCT04445428).

3 | THINKING AHEAD: LESSONS FOR THE POST-COVID SCIENTIST

In the past year, our understanding of the SARS-CoV-2 virus has expanded at a truly unprecedented rate. While the vaccines summarized here represent only a small fraction of the scientific accomplishments achieved by research groups working around the world—and around the clock—the strain this pandemic has brought to our global community sheds light on certain cracks in our system that must be addressed.

3.1 | Pandemics end, coronaviruses do not

SARS-CoV-2 shares about 80–90% sequence identity to SARS-CoV-1 (SARS),^{1,127} and about 50% sequence identity to MERS-CoV (MERS).¹ In addition, both SARS-CoV-1 and SARS-CoV-2 infect host cells by binding to the **angiotensin-converting enzyme 2** receptor via highly similar spike proteins. This level of conservation within members of the coronavirus family has allowed much of the knowledge gained during the 2002 SARS epidemic to be applied in the design of COVID-19 prophylactics and treatments. However, when SARS disappeared suddenly in the summer of 2003, interest and funding for further development of a vaccine or reliable treatment were redirected into other channels. Additionally, despite emerging in 2012 and being a serious health problem for certain parts of the world, there are still no vaccines or specialized treatments for MERS, possibly due to the lack of global interest. Given what is known about coronavirus cross-species transmission¹²⁸ and the simple fact that 3 of the 7 zoonotic coronaviruses to date are capable of significantly reducing our quality of life, it would be imprudent not to prepare for future coronavirus epidemics. Further research into coronaviruses and efforts to develop therapies must persist even after COVID-19 elimination so that communities may be more prepared to respond. Efforts to track the biology and evolution of other coronavirus strains should be made so that we may predict—and minimize—future animal-to-human transmission. Indeed, predictions of a second zoonotic SARS-CoV virus emerged as early as 2007,¹²⁹ but were largely ignored. With the right knowledge, preparation and support from scientifically driven policies, future coronavirus-based epidemic scan and should be mitigated.

3.2 | To stop viral spread, countries need to work together

Given the speed of SARS-CoV-2 transmission around the globe despite lockdown and travel restrictions, it is clear that no country will be safe from infection without concerted efforts worldwide. The success or failure of virus eradication policies depend largely on vaccine accessibility and distribution. For many low-income countries, the lack of infrastructure and funds necessary to acquire, transport, and administer vaccines can prevent disease eradication. For example, while the WHO-funded campaign to eradicate polio, which was launched in 1985, helped eliminate the disease within the Americas and Europe by 1994 and 2002 respectively, countries including Afghanistan, Pakistan, Nigeria and the Philippines continue to suffer outbreaks today.¹³⁰ In the case of COVID-19, this disparity will be even more serious, as developed countries have already established heavy monopolies on existing SARS-CoV-2 vaccine candidates. The necessity of a coordinated global effort to control viral spread cannot be over-stated, therefore, conversations must be held about SARS-CoV-2 in developing regions, and infrastructure to fund and monitor COVID-19 vaccination will be needed in these communities to facilitate timely global recovery.

This pandemic has also amplified existing challenges involving other viral pathogens. Thanks to the combination of viral persistence in developing countries and a souring attitude towards vaccination in certain developed countries, measles—which was eliminated from the USA in 2000—has since re-emerged. Last year, 1276 USA cases were reported, and cases are projected to rise in the coming years due to COVID-19 disrupting regular childhood vaccination schedules around the world.^{131,132} A similar narrative is predicted for polio, which, prior to the pandemic, was on track for eradication by 2021.¹³³ While not all viruses can be feasibly eradicated due to the presence of nonhuman reservoirs, long latency periods, or the lack of a vaccine conferring life-long immunity,¹³⁴ this is not the case for measles, polio and several other viral diseases. Therefore, to minimize the risk of what are entirely avoidable epidemics, we must take disease eradication seriously where it is applicable, and to do so, effort should be made to address vaccination policies both internationally and at home.

3.3 | To combat misinformation and facilitate public trust, increased scientific transparency is needed

Alongside the pandemic, communities around the world are being overwhelmed by misinformation regarding COVID-19, ranging from trivialization of health risks to downright fraudulent claims of cures and prophylactics.^{135,136} While we have been focusing our efforts on treating the pandemic, this *infodemic* has gone unchecked. Science communication and transparency is crucial to maintaining public trust, especially now, when each new COVID-19 report or finding is heavily scrutinized by the public eye. Currently, the relative obscurity and unusual speed by which drug companies and their academic partners complete trials, as well as concerns over possible political pressure on scientific judgement has both degraded the public's trust in treatments and vaccines and fuelled further misunderstanding. This can lead to noncompliance when a vaccine is eventually released, which can delay or prevent COVID-19 elimination.

Undoubtedly, there is a need for clearer communication during clinical trials. When AstraZeneca's viral vector vaccine ChAdOx1 nCov-19 was temporarily halted, this was reported to be due to neurological symptoms in a participant.^{48,49} However, when the pause was lifted in the USA, the only announcement made was that the FDA had reviewed the safety data and found it satisfactory.⁵⁴ Similarly, Johnson & Johnson's Phase III trial for Ad26.COV2.S was paused for about a week in October with no public report explaining either the reason for the hold or why it was lifted. The absence of official reports can fuel misinformation and mistrust, and while companies need to maintain the confidentiality of trial participants, they must also learn to be more proactive, transparent, and consistent with the public by announcing and explaining major decisions.

One way to prevent misinformation and foster trust is to make details regarding treatment design and clinical trials available to the broader community. So far, Moderna, Pfizer, AstraZeneca, and Johnson & Johnson have all published their Phase III trial protocols, and

the FDA has announced its intention to do the same with its scientific review process for COVID-19 EUAs.¹³⁷ These documents include details on data collection, participant pool size, known side effects, and how vaccine efficacy was determined. EU regulators are also making an effort to improve transparency around COVID-19 treatments. In particular, the European Medicines Agency is publishing all clinical data in support of applications for COVID-19 treatments, along with the full risk management plan generated by the European Medicines Agency's scientific committees' assessment which powers subsequent commission decision of treatment licensing.¹³⁸ Policies such as this foster public trust and promote science literacy over time. We therefore encourage other pharmaceutical companies and research groups to follow suit, and call for continued data transparency in the post-COVID-19 world.

3.4 | For future vaccine development, could mRNA be the answer?

Interim Phase III results have so far reflected a triumph for mRNA vaccines. To date, the Pfizer BNT162b2 and the Moderna mRNA-1273 vaccines are reported to be 95 and 94% effective, respectively, which is significantly higher than the minimal 50% efficacy required by the FDA. If commercialized, these would be the first approved vaccines using RNA. There are clear benefits to nucleic acid vaccines beyond their immunogenicity; unlike all other vaccine platforms, the nucleic acid vaccine production does not rely on live vaccine samples or other biological systems. Genomic material can be quickly and cheaply reproduced in a test tube, and only knowledge about its sequence is necessary for vaccine design. In theory, this minimalistic approach should also allow the same development pipeline to be applied to a large variety of pathogen targets, making this platform suitable for future vaccine development.

While the relative instability and inefficient delivery of nucleic material had previously limited the development of RNA vaccines, recent technological advances in lipid nanoparticle formulation have largely removed the latter barrier.⁷¹ Improvements to nanoparticle design and cold-chain distribution infrastructure are currently being made to address stability concerns, but unless significant progress is made, this vulnerability will probably limit the platform's ability to be used in most developing countries. Hopefully, future technological developments and efforts to concentrate RNA vaccine immunogenicity into a single dose¹³⁹ will negate some of these administrative challenges in the coming years. DNA vaccines are similarly inhibited by challenges in nuclear delivery, and efforts to improve gene gun technologies as part of COVID-19 DNA vaccine development are expected to significantly impact the future prospects of this platform.

Since RNA vaccines have not been commercialized before, little is known about their safety profile and long-term efficacy. So far, interim Phase III safety data have been largely positive, but these trials are unlikely to identify rare adverse effects due to limits in participant size and can only provide information on short-term effects observed in the last few months. Since the half-life of RNA material in the body

is only a matter of hours, and these vaccines do not contain any other viral material, these treatments are unlikely to trigger unexpected long-term adverse effects. However, little is known about the duration of its conferred immunity in the absence of long-term data. As it becomes more and more likely that an RNA vaccine for COVID-19 will be approved for emergency use, cautious vigilance must be maintained to determine the long-term efficacy and safety of these vaccines over the next months and years in order to determine the suitability of this platform for future vaccine development.

3.5 | Regulate accelerated vaccine development, maximize trial data output

When the FDA announced guidelines for accelerated vaccine development, a number of decisions, including study demographic groups, trial end points, and even the definition of mild vs severe COVID-19 cases were left to the discretion of pharmaceutical companies. This has resulted in small variations in trial design between companies, including the ages and health status of participants, and when to test for COVID-19 after treatment. While these variations do not negate the results from each individual study, they prevent different vaccines from being compared against each other, which is required to determine if certain vaccines are more suitable for certain populations. Normally, additional trials comparing different therapies using the same protocol are conducted, but during a pandemic, we lack the benefit of time.

One solution to this problem is to organize a single massive Phase III trial to simultaneously test various vaccines against COVID-19 and each other, such as that proposed by the WHO for the EU.¹⁴⁰ While this *Solidarity Trial* is theoretically beneficial and require fewer enrolled participants overall (as all vaccines share the same placebo group), the level of coordination required by all participating parties has led to undesirable delays. To make the most out of the limited efficacy and safety data that can be obtained during accelerated vaccine development, without obstructing testing, we propose that certain terms, expected outcomes, and important participant groups should be defined in advance by regulators. Since different therapies necessarily variate in dosing strategies and target populations, pharmaceutical companies should be allowed to opt out of certain defined study groups or endpoints that are inapplicable for their vaccine. Improving this infrastructure will help to facilitate accelerated vaccine development during a pandemic, ensure some level of comparability between different candidates, and help regulatory bodies make informed decisions.

4 | CONCLUSION

In this review, we summarized the current vaccine landscape for COVID-19 and provided an updated snapshot of this rapidly developing field. Understanding the mechanisms by which these vaccines function help us to not only better grasp the significance of these

clinical findings, but also appreciate the complexity of the efforts. As our global community will doubtlessly go on to face similar viral challenges in the future, we also identified a number of issues that need to be addressed so that we may be better prepared to respond to the next global viral challenge. The degree by which the scientific community has mobilized to study and develop effective treatments for COVID-19 has been remarkable. While it is our role as scientists to confront current challenges, we must also strive to protect our communities from future risks.

4.1 | Nomenclature of targets and ligands

Wherever applicable, the nomenclature in this work follows the guidelines set by IUPHAR/BPS.¹⁴¹ Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.¹⁴¹

ACKNOWLEDGEMENTS

The authors would like to thank Drs Ron Liem and Yinghui Mao (Columbia University, department of Pathobiology and Cell Biology) as well as Dr Marcella O'Reilly (Columbia University, Cardiometabolic Genomics Center) for providing valuable feedback on an earlier version of this manuscript. We also thank Dr Serge Cremers (Columbia University, department of Pathology) and Dr Muredach Reilly (Columbia University, Cardiometabolic Genomics Center) for their encouragement and advice. All diagrams in this work were created using BioRender.com.

COMPETING INTERESTS

There are no competing interests to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Calvo Fernández E, Zhu LY. Racing to immunity: Journey to a COVID-19 vaccine and lessons for the future. *Br J Clin Pharmacol.* 2021;87(9):3408-3424. <https://doi.org/10.1111/bcp.14686>